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Corticosteroids and Other Anti-Inflammatory Strategies in Pediatric Heart Surgery: A National Survey of Practice

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Background:

The role of steroids to mitigate the deleterious effects of the pediatric cardiopulmonary by-pass remains a matter of debate therefore we aimed to assess preferences in administering corticosteroids and the use of other anti-inflammatory strategies in pediatric cardiac surgery.

Methods

A 19-question survey was distributed to consultants in pediatric cardiac anesthesia from 12 centers across the UK and Ireland.

Results

Out of the 37 respondents (37/60, 62%): 24 (65%) use corticosteroids while 13 (35%) do not use steroids at all. We found variability within 5 out of the 12 centers (41%). Seven consultants (7/24, 29%) administer corticosteroids in every case while 17 in selected cases only (17/24, 71%). There was variability in the dose of steroid administration. Almost all consultants (23/24, 96%), administer a single dose at induction and one administers a two-dose regimen (1/24, 4%). There was variability in corticosteroid indications. Most consultants (24/37, 66%), use modified ultrafiltration at conclusion of cardiopulmonary bypass. Fifteen consultants (15/32, 47%) report the use of aprotinin while only 3 use heparin coated circuits (3/24, 9%).

Conclusions

We found wide variability in practice in the administration of corticosteroids for pediatric cardiac surgery, both within and between units. While most anesthetists administer corticosteroids in at least some cases, there is no consensus on the type of steroid, the dose and at which patient groups this should be directed. Modified ultrafiltration is still used by most of the centers. Almost half of consultants use aprotinin while heparin coated circuits are infrequently used.

Introduction

Prophylactic corticosteroids (CS) in pediatric heart surgery using cardiopulmonary bypass were introduced in clinical practice almost 60 years ago ¹. Despite their long-term use, there is ongoing debate regarding their impact on clinical outcomes. Corticosteroids are still given prophylactically to dampen the systemic inflammatory response syndrome (SIRS) to the extracorporeal circuit. The SIRS results from the contact of the various blood components with cardiopulmonary bypass (CPB) circuit, the endothelial cell insult and the associated ischemic reperfusion injury ². In children, these changes are more profound due to the surface of the extracorporeal circuit relative to their small circulating blood volume, the more frequent use of the deep hypothermic circulatory arrest (DHCA) and more pronounced hemodilution ³. However, according to the available evidence, it is unclear if attenuation of the inflammatory response ultimately translates into better clinical outcomes ⁴⁻⁷. Is inflammation an adaptive or a maladaptive process? The available randomized controlled trials of steroid versus placebo suffer from small sample sizing. This precludes the detection of a significant treatment effect on the clinical endpoints ^{4,6,8-14}. The results of an ongoing, large randomized controlled trial (RCT) of CS versus placebo in 1200 neonates are still awaited and hopefully will inform us more on this matter¹⁵. Notably, two very large registry studies showed no benefit in steroid use in pediatric heart surgery and raised concerns regarding infection ^{16,17}. Furthermore, the long-term impact of CS in pediatric heart surgery to the developing child is unknown due to the lack of long term follow-up studies. A particular concern is the potential deleterious effect on neurocognitive development observed in other patient groups ^{18,19}.

Corticosteroids are also used to protect against relative adrenal insufficiency that could potentially occur perioperatively and result in hemodynamic compromise. However, very little is known about the physiology of the hypothalamic pituitary adrenal (HPA) axis in children undergoing surgery ^{20,21}. How do we define adrenal insufficiency in children undergoing heart surgery? Certainly, the use of random time point measurements or various adrenal stimulation

tests are likely to be inaccurate in the context of a known dynamic, pulsatile HPA axis activity perioperatively ²².

Another cited justification for corticosteroid administration is their neuro-protective effect in complex surgical cases undergoing deep hypothermic circulatory arrest (DHCA). The evidence in this area is limited to animal studies and it is conflicting ^{23,24}.

In view of the existing lack of either evidence or consensus, our survey was designed to assess current preferences consultant anesthetists in the UK to administer steroids in pediatric heart surgery with cardiopulmonary bypass. As a secondary objective, we also surveyed the use other anti-inflammatory strategies including modified ultrafiltration, aprotinin and heparin coated circuits.

Material and Methods

A 19-question survey was distributed to the Congenital Cardiac Anesthetic Network (CCAN) UK consultant email list. It is estimated that 70-80 doctors practice pediatric cardiac anesthesia in the UK and CCAN is a network of these doctors ²⁵. The responses were collected during December 2015-November 2016 period and several reiterations were conducted until an adequate response from all units was received. Results were collected using the Survey Monkey Inc. platform, San Mateo, California, USA and analyzed using Graph Pad Prism version 7.00 for Windows, La Jolla California USA.

Results

The survey was sent to 60 consultants from all 12 National Healthcare System units across the UK and Ireland performing pediatric heart surgery. We received 37 responses (61.7%) with an average of 3 responses per center (ranging from 1 to 5 responses). In 5 out of the 12 centers, the practice of administering steroids varied between consultants within that

centre (Figure 1 B). Out of the 37 respondents from UK and Ireland: 24 (64.8 %) reported the use of CS while 13 (35.1%) do not use CS at all. Seven (7/24, 29.1%) anesthetists administer CS in every case while 17 (17/24, 70.8%) in selected cases only (Figure 1 A).

There were 29 indications cited for steroid use in total, ranging from 1 to 6 indications per respondent (n=17). The most common indications for corticosteroid administration was surgery in neonates (9, 31%), surgery with use of DHCA (9, 31%), re-do cases (2, 6.9%), the Norwood operation (2, 6.9%), high perioperative inotrope requirement (2, 6.9%), complex atrial/ventricular septal defects (2, 6.9%), switch operation (1, 3.4%), long CPB time (1, 3.4%) and surgery in infants (1, 3.4%)

The most widely used corticosteroid was dexamethasone used by 17 consultants (17/24, 70.8%) followed by methylprednisolone used by 4 (4/24, 16.7%) and hydrocortisone used by 3 consultants (3/24, 12.5%). Almost all consultants (23/24, 95.8 %,) administer a single dose of steroid at induction and only one (1/24, 4.2%) administers a two-dose regimen (dose at induction and one at 6 hours from the first dose). Dexamethasone doses ranged from 0.5mg/kg to 1 mg/kg, methylprednisolone dose ranged from 20mg/kg to 30mg/kg and hydrocortisone was administered at a dose of 4mg/kg (Table 1, Supplementary file). If we calculate the equivalent anti-inflammatory dose of dexamethasone for the rest of CS administered, there is further variation with dexamethasone doses ranging from 0.15 mg/kg up to 5.62 mg/kg (Table 1, Supplementary file), ²⁶.

Most consultants (24/37, 65.9%) use modified ultrafiltration at conclusion of cardiopulmonary by-pass. Seven consultants (7/24, 29.25%) use ultrafiltration in children up to 6kg, 13 (13/24, 54.2%) in children up to 10 kg and 4 consultants (4/24, 16.7%) in children over 10 kg. Out of the 32 respondents: 15 (15/32, 46.9%) consultants use aprotinin and only 3 (3/24, 9.4%) heparin coated circuits.

Comment

Across the UK and Ireland approximately 4500 pediatric heart operations involving cardiopulmonary by-pass are performed every year²⁷. Therefore, understanding the impact of steroids on clinical outcomes is an important health issue. In contrast to previous surveys^{28,29}, we have also assessed the preference of steroid administration not only *between* centers but also *within* centers. In the survey by Checchia et. al 36 responses were returned from each center representative²⁹ and in the survey by Allen et al.²⁸ only 12 responses were returned in total from center representatives. Neither study looked at variation within centers. In our survey, we found variation in steroid preferences within 5 centers. This suggests the lack of local consensus between consultants and a lack of protocols in certain centers.

Most consultant anesthetists use CS in pediatric heart surgery (65%) in some form. However, we noticed a trend in reduced CS use compared to an international survey by Checchia et al.²⁹ from 2005 (97%) and an older UK survey by Allen et al.²⁸ (80%). Out of the consultants that use CS, the majority administer them in selected cases only (71%) compared to 60% and 58% in the previous surveys of practice^{28,29}. This trend towards reserving CS for selected cases reflects the ongoing lack of consensus and need for further evidence in the “high risk” patient groups.

We found variability in the indications of CS use. The most common indications for steroid use were surgery in neonates (31%) and use of DHCA (31%). Certainly, we know very little about the stress response in neonates. The immaturity of their HPA axis means they are less likely to cope with the stress of surgery²¹. We conducted a recent systematic literature review focused on this group and found a limited evidence¹². The use of CS for neuroprotection in cases with use DHCA is another unanswered question. The available studies assessing the effect on brain protection used piglet cardiopulmonary by-pass models. A study by Langley et al. suggested cerebral protection if methylprednisolone (MP) is given early: 8 to 12 hours pre-

operatively²³. On the other hand, a study by Schubert et al.³⁰ showed no benefit for MP 24-hour pre-treatment. Other indications for CS were aimed at the high-risk procedure groups. There are a few studies in this group and the evidence is again conflicting. In a small RCT of 20 neonates undergoing arterial switch, pre-treatment with MP reduced the expression of myocardial and plasma cytokines that translated in lower inotrope requirement and decreased myocardial damage⁶. A large retrospective analysis of 549 neonates who underwent the Norwood procedure found intraoperative steroid administration was not associated with improvement in outcome. Furthermore, steroid non-recipients had better hospital survival, but longer intensive care and hospital stays³¹. With regards to inotrope requirements, there is some evidence that so-called “rescue” steroids improve hemodynamics and lower inotrope requirement³². In a RCT of 40 neonates by Roberto et al the use of a prophylactic postoperative steroid infusion reduced inflammation, improved fluid balance and urine output and allowed a faster wean from catecholamines or vasopressin¹⁴. Similar to our survey of prophylactic steroid administration, a recent survey by Flores et al.³³ found significant variability in the indications for corticosteroid administration in patients with severe low cardiac output syndrome.

We found variation in both the type of steroid used and in terms of the doses administered. This is a similar finding to previous surveys of practice^{28,29}. Almost all consultants give one dose at anesthesia induction and only one reported to administer a two-dose regimen at induction and at 6 hours from the first dose. A few studies on piglet cardiopulmonary by-pass models found some benefit of early CS administration on pulmonary function³⁴ and brain protection²³. However, in an RCT of 76 neonates Graham et al. found a two-dose regimen (8 hours pre-operative and operative) reduced the pre-operative interleukin-6 cytokine concentration two-fold compared to the single-dose steroid arm. There was no difference in postoperative cytokines or clinical outcomes between the single and two dose regimens³⁵. In contrast to US practice, where steroids are administered in the majority of the cases in the prime³⁶, in our survey we noted that steroids are given most of the time pre-

operatively, at induction. A three-arm RCT of 45 children evaluated the effect of methylprednisolone administration in prime versus intravenously (at induction) during cardiac surgery. There was no difference in terms of clinical outcomes between the three groups, however, steroids given at induction were superior in terms of anti-inflammatory effect compared to the prime route¹¹.

Modified ultrafiltration use in pediatric heart surgery can remove the excess of water and inflammatory mediators during cardiopulmonary by-pass. The impact on postoperative course is hemoconcentration, reduced need for transfusions, and improvement of cardiac and respiratory function³⁷. According to previous surveys, its use amongst pediatric heart surgery centers ranged from 75-80%^{28,29}. In the current survey, fewer centers used MUF (e.g. 66%). This could be explained by the emergence of low prime volume extracorporeal circuits, avoidance of severe hemodilution or efficient use of conventional ultrafiltration that no longer justifies the use of MUF and its associated risks³⁸. Aprotinin is a potent anti-fibrinolytic but has also anti-inflammatory properties that could be advantageous in pediatric heart surgery. However, its safety profile in both adult and pediatric patients remains a matter of debate³⁹. This is reflected in the current survey where almost half of the consultant reported its use. Very few centers use heparin coated circuits.

There are no studies to date investigating the combined effect of the various anti-inflammatory modalities.

The strengths of the current study are the analysis of steroid variation within centers and of steroid indications for the various patient groups. The weakness of this study is its response rate of only 61.7 %. However, this compares to previous surveys on this topic. Another source of bias could be steroid administration by other healthcare professionals including surgeons, intensivists or perfusions. However, within UK, the prophylactic, perioperative steroid administration is usually governed by the pediatric cardiac anesthetist.

The current survey offers the following observations. The use of prophylactic corticosteroids in pediatric heart surgery remains a matter of intense debate. We found variations in steroid administration both within centers and between centers. Most consultant anesthesiologists surveyed give steroids in selected cases. However, there was heterogeneity in the cited indications, dose and type of steroid used. Of those that used steroids, almost all administer a single dose of CS preoperatively at induction. These results reflect the lack of evidence from placebo controlled randomized trials of CS versus placebo, powered to look at the impact on clinical outcomes. In the context of the low mortality and morbidity associated with pediatric heart surgery, the obstacle to conducting such research is the recruitment of a sufficiently large sample size to detect any effect. This also implies that effect size of corticosteroid use is small across a population or may be limited to selected pathologies. This survey also highlights the need to investigate the role of steroids in the “vulnerable” patient groups such as neonates or complex surgical cases with use of deep hypothermic circulatory arrest.

Disclosures

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2. No conflict of interest.

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Figure Legends

Figure 1 Corticosteroid preferences (1 A) variation within and between centers (1B)



